

	Type	Hits	Search Text
1	BRS	17680	polysorbate
2	BRS	118	S1 near5 pharmaceutical
3	BRS	52	S2 and enzyme
4	BRS	7	acetyl near2 galactosamine near2 sulfatase
5	BRS	2429	(asb or arsb or arylsulfatase)
6	BRS	326	S5 and (polysorbate or tween or sorbitan)
7	BRS	292	S6 and (mps or therapy)
8	BRS	53	S6 and (mps or msd or maroteaux)
9	BRS	571	mucopolysaccharidoses or mucopolysaccharidosis
10	BRS	152	S9 and (sulfatase or asb or arsb or arylsulfatase)
11	BRS	99179	polysorbate or sorbitan or tween
12	BRS	0	S11 near10 (enzyme near3 therapy)
13	BRS	0	S11 near20 (enzyme near3 therapy)
14	BRS	398	S11 and (enzyme near3 therapy)
15	BRS	87	S11 and (enzyme near2 replacement near2 therapy)
16	BRS	1432	(polysorbate or sorbitan or tween) [TI]
17	BRS	0	S16 and (enzyme near2 replacement near2 therapy)
18	BRS	107	S16 and (therapy or drug or pharmaceutical)
19	BRS	79	S16 and (pharmaceutical)
20	BRS	78	S16 and (pharmaceutical)
21	BRS	15	"6426208"
22	BRS	350	enzyme near2 replacement near2 therapy
23	BRS	87	S22 and (polysorbate or tween or sorbitan)
24	BRS	0	S22 near20 (polysorbate or tween or sorbitan)
25	BRS	0	S22 near30 (polysorbate or tween or sorbitan)
26	BRS	0	S22 near (polysorbate or tween or sorbitan)



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## Typed Drawing

Word Mark	ARYPLASE
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***What is MPS VI?***

MPS VI (also known as Maroteaux-Lamy Syndrome) is a genetic disease caused by the deficiency of N-Acetylgalactosamine 4-sulfatase (also referred to as arylsulfatase B), an enzyme normally required for the breakdown of certain complex carbohydrates known as glycosaminoglycans (GAG). If the enzyme is not present in sufficient quantities, the normal breakdown of GAG is incomplete or blocked. The cell is then unable to excrete the carbohydrate residues and they accumulate in the lysosomes of the cell and cause MPS VI.

***What Happens to Patients with MPS VI?***

About 1,100 patients in developed countries have MPS VI. Patients with MPS VI are usually diagnosed by one to five years of age. After diagnosis, the patients get progressively worse leading to severe disability and early death. During the course of the disease, the build-up of GAG results in one or more of the following symptoms:

- Inhibited growth
- Impaired vision and hearing
- Frequent ear and lung infections
- Impaired cardiovascular and heart function
- Upper airway obstruction and reduced pulmonary function
- Enlarged liver and spleen
- Joint deformities and reduced range of motion
- Sleep apnea
- Malaise and reduced endurance

***How is MPS VI Currently Treated?***

Most patients are treated symptomatically only and do not receive specific therapy to treat the underlying cause of MPS VI. Currently, the only treatment for MPS VI is a bone marrow transplant (BMT), primarily performed in young, more severely affected patients. BMT, however, poses some challenges. Some patients cannot find an appropriate bone marrow donor, and of those who do, some choose not to undergo the procedure because of the associated risks and side effects.

***How is BioMarin Treating MPS VI?***

Last updated: 7/15/2004

***What is Aryplase™?***

Aryplase, a specific form of recombinant human N-acetylgalactosamine 4-sulfatase (also known as arylsulfatase B), is an investigational enzyme replacement therapy for the treatment of mucopolysaccharidosis VI (MPS VI).

MPS VI, a genetic disorder affecting approximately 1,100 patients in the developed world, is characterized by a deficiency of N-acetylgalactosamine 4-sulfatase, an enzyme normally needed to breakdown certain complex carbohydrates known as glycosaminoglycans (GAG). Without sufficient quantities of this enzyme, the normal breakdown of GAG is incomplete or blocked. The carbohydrate residue then accumulates in the lysosomes of the cell, giving rise to MPS VI. Aryplase is designed to address the underlying cause of MPS VI and deliver the enzyme that MPS VI patients are lacking.

***What is the Development and Regulatory Status of Aryplase?***

In June 2004, BioMarin announced positive results from the Phase 3 trial of Aryplase for the treatment of MPS VI. Based on these data, the company expects to file for United States and European Union marketing authorization in the fourth quarter of 2004.

BioMarin has received orphan drug and fast track designations for Aryplase from the U.S. Food and Drug Administration (FDA). Additionally, the European Commission (EC) has designated Aryplase for the treatment of MPS VI as an orphan medicinal product in the EU.

***What Data Exist on the Treatment of MPS VI Patients with Aryplase?*****Phase 3 Data**

In June 2004, BioMarin announced data from its Phase 3 multi-center, double-blind, placebo-controlled trial of Aryplase. The trial, which was designed to evaluate the safety and efficacy of Aryplase, enrolled 39 patients, ranging in age from 5 to 29 years, at six sites located throughout the world. Patients were randomized on a one-to-one basis into one of two groups: an Aryplase treatment group or a placebo control group. Each group received a weekly intravenous infusion of 1.0 mg/kg of either Aryplase or placebo solution for 24 consecutive weeks. During the 24-week period, 19 patients received weekly intravenous infusions of Aryplase and 20 patients received weekly placebo infusions. One patient in the placebo group dropped out of the trial for reasons unrelated to treatment.

Patients were evaluated at pre-defined, six-week intervals to assess changes in primary and secondary efficacy endpoints and the safety and tolerability of weekly Aryplase infusions. Results of the trial are summarized below:

- The clinical trial demonstrated a statistically significant improvement in endurance ( $p=0.025$ ) in patients receiving Aryplase compared to patients receiving placebo as measured by the distance walked in 12 minutes, the primary endpoint in the trial.
- The data from the trial demonstrated a statistically significant reduction in glycosaminoglycans (GAGs) excreted in the urine ( $p<0.001$ ) in patients receiving Aryplase compared to patients receiving placebo. GAG reduction was one of two secondary

endpoints measured in the clinical trial. The 3-minute stair climb, another measure of endurance and also a secondary endpoint, demonstrated a positive trend ( $p=0.053$ ) in patients receiving Aryplase compared to patients receiving placebo.

- The results of the clinical trial indicate that treatment with Aryplase was generally well-tolerated. Adverse events during infusions were more common in patients receiving Aryplase but were generally mild to moderate in nature. The frequency of serious adverse events was more common in the placebo group.

### **Long-term Results from Phase 1 and Phase 2 Studies**

In November 2003, BioMarin reported encouraging long-term results from Phase 1 and Phase 2 clinical studies of Aryplase in patients with MPS VI. Long-term data from both studies indicate that Aryplase is generally well-tolerated and that patients continue to benefit from Aryplase treatment.

### **Phase 2 Long-term Results**

The Phase 2 open-label study enrolled 10 patients with MPS VI and evaluated a dose of 1.0 mg/kg, the higher of two doses investigated in the Phase 1 dose-ranging study. The study enrolled patients at two sites, one in the US and one in Australia. Data following 24 weeks of treatment with Aryplase were reported in March 2003. Results after 48 weeks of treatment with Aryplase are summarized below:

- Endurance as measured by distance walked in 12 minutes improved by an average of 139 percent (211 meters) over the baseline distance. This represents an average incremental improvement of 56 meters over the improvement observed after 24 weeks of Aryplase treatment. The 12-minute walk test is the primary endpoint in the current Phase 3 clinical study of Aryplase.
- Endurance as measured by the number of stairs climbed in three minutes increased by an average of 147 percent (61 stairs) over the baseline number. This represents an average incremental improvement of an additional 13 stairs over the improvement observed after 24 weeks of Aryplase treatment. The 3-minute stair climb is a secondary endpoint in the current Phase 3 study.
- Urinary GAG level, another secondary endpoint in the current Phase 3 study, was reduced by 76 percent on average after 48 weeks of treatment with Aryplase. Reduction in GAG level was 71 percent after 24 weeks of treatment with Aryplase. GAG, the carbohydrate residue that accumulates in tissues of patients and causes MPS VI disease, is a biomarker for enzyme activity *in vivo*.
- Sustained improvements were also observed in joint pain and stiffness, and variable improvements were observed in joint range of motion. Reduction in liver and spleen size was observed in all five patients presenting with hepatosplenomegally at baseline, and four of the five now have liver volumes in the normal range. Pulmonary function improvements were observed in several patients, primarily between 24 and 48 weeks.

### **Phase 1 Long-term Results**

The randomized, double-blind, Phase 1 study initially investigated two doses of Aryplase (0.2 mg/kg and 1.0 mg/kg) in two groups of three patients. Following positive results (announced in September 2001) after 24 weeks of treatment, all six patients continued to receive treatment at 1.0 mg/kg in an open-label extension study. Results after 96 weeks of treatment are summarized below:

- Endurance as measured by the distance walked in six minutes improved by an average of 96 percent (120 meters) over baseline after 96 weeks of therapy. Gains in the 6-minute walk test were maintained or improved from week 48 to week 96 for the four evaluable patients in the study at the 96-week time point.
- Urinary GAG level was reduced by 75 percent on average after 96 weeks of treatment. Patients who initially received the lower of the two doses experienced an incremental decrease in GAG level after receiving treatment with the higher dose.

### **Initial Results from Phase 1 and Phase 2 Studies**

#### **Phase 2 Results Following 24 Weeks of Treatment**

In March 2003, BioMarin announced data from a 24-week, open-label, international, multicenter Phase 2 clinical study of Aryplase in 10 MPS VI patients. Results from this Phase 2 study indicate that Aryplase is well tolerated and was associated with improvements in several clinical endpoints. The results of this study are summarized below.

- The average improvement at 12 minutes in the walk test was 155 meters over baseline distances, which ranged from 33 to 475 meters. On average, subjects demonstrated a 98 percent improvement in distance walked after 12 minutes.
- The average improvement at the six-minute time point of the 12-minute walk test was 64 meters over baseline distances, which ranged from 19 to 247 meters. On average, subjects demonstrated a 62 percent improvement in distance walked at six minutes.
- The average improvement in the number of stairs climbed in three minutes was 48 stairs over the baseline number, which ranged from 20 to 92 stairs. This increase in the number of stairs climbed represents an average improvement of 109 percent over baseline.
- Functional improvements were also observed in joint pain and stiffness, and in shoulder flexion, extension, and rotation in subjects who exhibited less than 90 degrees shoulder flexion at baseline.
- In addition to the clinical improvements observed, study participants also demonstrated an average decrease in urinary GAG excretion of 71 percent.

#### **Phase 1 Results**

In September 2001, BioMarin reported results from a Phase 1 randomized, double blind six-patient clinical trial of Aryplase. The primary objective of this trial was to evaluate the safety of Aryplase at two dose levels: 0.2 mg/kg and 1.0 mg/kg. The enzyme was well tolerated by all six patients during the 24-week treatment stage.

There were no treatment-related serious adverse events and no significant allergic reactions to the enzyme infusions. In addition, urinary glycosaminoglycan (GAG) excretion was reduced by a mean of 70 percent and 55 percent in the high and low dose groups, respectively. Furthermore, reduced urinary GAG excretion was evident within three weeks of initiating treatment.

### **Safety Data for Phase 1 and Phase 2 Studies**

Aryplase was generally well-tolerated during both the Phase 1 and Phase 2 clinical studies. In the Phase 1 study, after nearly two years of treatment during which patients underwent 508 infusions, there was one serious adverse event (SAE) that the investigator attributed as related to drug. There were 46 mild, four moderate, and no severe drug-related adverse events (AE). Fever and dermatitis were most commonly observed. In the Phase 2 study, out of 475 infusions, there was one SAE, an asthma attack, which the investigator attributed as possibly related to drug. A total of 31 infusion-related AEs were attributable to the drug, 18 of which were mild skin hypersensitivity reactions in one patient, and four similar incidences in a second patient. Most patients in both studies developed antibodies to Aryplase although antibody presence did not correlate with clinical safety or efficacy. Additionally, approximately 1.5 years after initiating treatment, relative antibody levels for all patients involved in the Phase 1 study fell to levels slightly above background.

Last updated: 7/15/2004



## BioMarin Initiates Phase I/II Clinical Trial of Enzyme Replacement in MPS-VI Patients

**PRNEWswire**

NAVATO, California, Oct. 12 /PRNewswire/ -- BioMarin Pharmaceutical Inc. announced the initiation of a Phase I/II clinical trial of recombinant human Arylsulfatase B (rhASB), also known as recombinant human N-acetylgalactosamine-4-sulfatase, in enzyme replacement therapy for patients with Mucopolysaccharidosis (MPS) VI. MPS-VI is a progressive, chronically debilitating genetic disease that results in early death. The Phase I/II trial follows successful completion of preclinical studies of rhASB that were conducted in a naturally-occurring feline model of MPS VI disease. The FDA has granted BioMarin orphan drug designation and fast track designation for rhASB for the treatment of MPS-VI. RhASB is manufactured by BioMarin at a GMP facility licensed by the State of California.

Grant W. Denison, Jr., Chairman and Chief Executive Officer of BioMarin stated, "The start of a clinical trial for a second MPS disease is a major milestone for BioMarin. It represents the successful leveraging of our enzyme replacement therapy experience gained with Aldurazyme (TM), which is being investigated in patients with MPS-I. Positive preclinical results of Aldurazyme in a naturally-occurring canine model of MPS-I predicted positive clinical results in a recent Phase I/II clinical trial of Aldurazyme. We believe that positive preclinical results of rhASB in a naturally-occurring feline model of MPS-VI will predict a positive outcome for the Phase I/II clinical trial of rhASB."

### The Clinical Trial

The Phase I/II clinical trial is designed to investigate the safety and efficacy of rhASB for the treatment of MPS-VI in a randomized, double-blinded study at two dose levels. Six patients will receive weekly intravenous infusions. The patient evaluation period will be 24 weeks. The primary objective of the trial will be to measure safety of rhASB. In addition, the trial will evaluate efficacy of the treatment based on several physical, biochemical and functional parameters known to be severely affected by the disease. Paul Harmatz, M.D., of the Children's Hospital Oakland, Oakland, California, who is the principal investigator for the study, stated, "We're excited to be part of this historic study for MPS-VI patients. We hope that enzyme replacement therapy will provide substantial benefit to patients who currently have few treatment options."

### The Disease

MPS-VI (also known as Maroteaux-Lamy syndrome) patients are deficient in ASB enzyme that is required for the progressive, stepwise breakdown of certain complex carbohydrates. This deficiency results in the progressive build-up of carbohydrate



residues in the lysosomes in all cells of the body. Patients are typically diagnosed at 6 to 24 months of age when they initially show various symptoms of the disease. Symptoms characteristically include deceleration of growth, enlarged liver and spleen, skeletal and joint deformities, and upper airway obstruction. Life-threatening cardiopulmonary problems often develop in the teenage years and many patients do not survive past 20 to 30 years of age, particularly in the more severe cases of the disease. Patients with the milder cases of the disease may live longer but with significant medical problems. The symptoms of MPS-VI are similar to those of MPS-I; however, the mental retardation associated with the severe form of MPS-I has not been reported for patients with MPS-VI. Bone marrow transplantation is a treatment option for some patients, but this procedure is often associated with significant risk. MPS-VI afflicts approximately 1,100 patients in the developed world.

### Preclinical Studies

Seven separate preclinical studies of rhASB have been conducted in a naturally-occurring feline model of MPS-VI disease. Treatment was associated with clearance of the accumulated carbohydrate residues from all of the major organs along with an increase in bone mineral volume, greater mobility and flexibility, and improved neurological symptoms. The preclinical studies were conducted by a leading researcher in the field, Dr. John Hopwood, Professor and Head of the Lysosomal Diseases Research Unit, Women's and Children's Hospital, Adelaide, Australia. Dr. Hopwood stated, "The MPS-VI felines have many of the same clinical symptoms that are seen in human patients. Following enzyme replacement with rhASB, we have observed stabilization and improvement in many of these symptoms. I am very pleased that our work in preclinical testing is now being advanced to testing this promising therapy in the clinic."

### Regulatory Status

The FDA has granted BioMarin orphan drug designation and fast track designation for rhASB for the treatment of MPS-VI. If BioMarin is the first company to gain market approval, orphan drug status will allow the Company to have market exclusivity for rhASB in the US for seven years following FDA approval. Fast track designation is granted to products in development for serious and life-threatening diseases. It allows the Company the option to file a "rolling" marketing application (Biologics License Application or BLA) and indicates that the BLA will likely receive an expedited review over six months rather than a normal review over a longer time. In addition, an application for orphan designation in the European Community was filed and is currently under review. Orphan designation in Europe allows for ten years of marketing exclusivity after approval of a marketing application

(Marketing Authorization Application or MAA).

BioMarin Pharmaceutical Inc. specializes in the discovery, development and commercialization of therapeutic products using carbohydrate-active enzymes. Since inception in 1997, BioMarin has applied its proprietary enzyme technology to the development of products in four therapeutic areas: genetic diseases, burn debridement, systemic fungal infections, and inflammation (psoriasis). Glyko, Inc., a BioMarin subsidiary, provides analytical and diagnostic products and services in the technological area of carbohydrate biology.

This press release contains forward-looking statements about the business prospects of BioMarin Pharmaceutical Inc. including potential products in different areas of therapeutic research and development and the progression of BioMarin products into clinical trials. In particular, this release indicated the potential for favorable results from rhASB, one of its enzyme product candidates, in a Phase I/II clinical trial of enzyme replacement therapy in

MPS-VI. Results of this trial may differ materially due to many factors including, without limitation, enzyme efficacy and safety, trial design and execution, and the predictive utility of certain animal models of disease. In general, BioMarin's overall results may differ materially depending on the progress of BioMarin's product programs, actions of regulatory authorities, availability of capital, future actions in the pharmaceutical market, developments by competitors, and those factors detailed in BioMarin's filings with the Securities and Exchange Commission such as 10-Q, 10-K and other reports.

SOURCE: BioMarin Pharmaceutical Inc.

ST: California

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*Posted October 12, 2000.*

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